

### **REMARKS**

Upon entry of the foregoing amendments, claims 4, 5, 7, 12, 16, 32-35 and 37 will be pending in the application. Claim 37 is the only independent claim.

#### **Explanation of and Support for the Amendments**

The paragraph bridging pages 15 and 16 of the clean copy of the substitute specification has been amended to correct a printing artifact where an open box was inadvertently printed instead of the Greek letter  $\beta$ , which was correctly printed in the marked-up copy of the substitute specification as filed with the Preliminary Amendment simultaneously filed with the filing of the present application.

Similarly, the paragraph bridging pages 17 and 18 and the two indicated paragraphs at page 18 of the clean copy of the substitute specification has been amended to correct a printing artifact where an open box was inadvertently printed instead of the Greek letter  $\mu$ , which was correctly printed in the marked-up copy of the substitute specification as filed with the Preliminary Amendment simultaneously filed with the filing of the present application.

Independent claim 37 has been amended to recite that the composition “consists essentially of,” rather than “comprises,” the indicated ingredients in the indicated concentrations or amounts. Claim 37 also has been amended to include in the claimed composition ranges for the amount of sulfobutylether  $\beta$ -cyclodextrin (SBE-CD), the amount of chitosan, a salt, or a derivative thereof formed by bonding acyl and/or alkyl groups with the hydroxyl groups, but not the amino groups of chitosan or a salt of the derivative thereof (for simplicity, chitosan and its claimed salts and derivatives will be referred to hereinafter as “chitosan”). The pH and viscosity of the composition have also been claimed in claim 37. In view of the amendments made to claim 37, the range for the amount of SBE-CD in claim 12 has been modified and claims 13 and 15 cancelled.

Support for the ranges for the amount of SBE-CD can be found at page 5, lines 11 to 13, of the substitute specification as filed. Support for the amount of chitosan can be found at page 8, lines 10 and 11, of the substitute specification as filed. Support for the pH range can be found

at page 8, lines 25 to 27, of the substitute specification as filed. Support for the viscosity range can be found at page 9, lines 1 and 2, of the substitute specification as filed.

Dependent claims 4, 7, 12 and 16 also have been amended to be consistent with the “consists essentially of” recitation now in independent claim 37.

Non-elected dependent claim 36, directed to a nasal drug delivery device or a dose cartridge for use in a nasal drug delivery device comprising a composition as defined in claim 37, has been cancelled without prejudice to its inclusion in one or more related applications.

Since the amendments are fully supported by the application as filed and contain no new matter, entry of the foregoing amendments is respectfully requested.

### **The Invention**

In order to understand the differences between the invention claimed in the present application and the cited references, it is critical to have a clear understanding of the claimed invention and the significance of the ingredients, including the amounts or concentrations of the ingredients, and the characteristics of the invention, especially when compared to the ingredients of the cited references.

Claim 37 now includes a concentration range for each of the ingredients of which the composition essentially consists. The pH and viscosity ranges have been added to emphasize that it is a combination of all of the ingredients and claimed characteristics that provides a composition with advantageous properties for the intranasal delivery of a zolpidem or a pharmaceutically acceptable salt thereof (for simplicity, zolpidem or its pharmaceutically acceptable salt will be hereinafter referred to as “zolpidem”).

The requirements for formulating a suitable composition for intranasal drug delivery are quite specific. Solutions for intranasal drug delivery are typically administered as a spray. It is therefore essential that the compositions of the invention have a viscosity which enables them to be sprayed.

The pH must be carefully selected, as the pH can have a significant effect on the solubility of the components of the composition and on the stability of the composition. The pH

of the composition must also be such that the composition is not irritating to the nasal mucosal after application.

The concentration of the drug is very important because the amount of liquid that can be administered to the nasal cavity is very limited. As discussed in the paragraph bridging pages 13 and 14 of the substitute specification as filed, a maximum of about 0.2 ml can be delivered to each nostril at one time. As explained in that paragraph, the concentration of the drug has a significant effect on the volume of the composition that needs to be administered.

It is not a simple and straightforward matter to select the combination of ingredients and the concentration of each of those ingredients that will provide a composition that is stable on storage, has a pH and viscosity suitable for nasal administration, can be delivered in a suitable volume and provides a bioavailability that allows the desired therapeutic effect.

The inventors have surprisingly found that a composition comprising each of the essential components in an amount within the ranges specified in claim 37 has the required combination of properties. As was pointed out in the last sentence of paragraph 8 of the Declaration of Jonathan David Castile Under 37 C.F.R. § 1.132, of record in the prosecution of this application ("Dr. Castile's Declaration"), there were unpredictable effects regarding zolpidem and the active ingredient in combination with SBE-CD and chitosan.

When preparing compositions for the intranasal delivery of zolpidem the solubility of zolpidem is a big issue and the pH of the solution can severely limit solubility.

Table 4 at page 22 of the present application illustrates the issues. In the absence of a cyclodextrin, it was not possible to obtain a stable solution comprising 20 mg/ml or even 15 mg/ml of zolpidem tartrate at pH 4. Stable solutions were only obtained at a lower pH or at a lower zolpidem concentration. In other words, it is clear from Table 4 that it is not possible to prepare a solution containing 16 mg/ml of zolpidem base (equivalent to 20 mg/ml of zolpidem tartrate) without using a cyclodextrin.

Cyclodextrins are known as compounds which are able to increase the solubility of drug compounds. However, not all cyclodextrins are equal and not all drug compounds are equal. Moreover, different cyclodextrins have different effects on the solubility of different drugs. Thus, the cyclodextrin that gives optimum solubility of one drug will not necessarily give

optimum solubility of another drug. See paragraph 9 of Dr. Castile's Declaration for support for both of these points.

As additional evidence of the varying effect of different cyclodextrins on a drug, the Examiner's attention is directed to enclosed U.S. Patent 7,423,026 ("Järvinen") which describes the use of specific types of cyclodextrins to solubilize cannabinoid compounds. At column 3, lines 38 to 40, of Järvinen it is stated that "the invention is based on the finding that methylated  $\beta$ -CDs increased the aqueous solubility of cannabinoids significantly more than other CDs". It is also stated that "the complexation of cannabinoids with methylated  $\beta$ -CD is more efficient compared to HP- $\beta$ -CD" (column 4, lines 9 to 11) and "methylated  $\beta$ -CDs offer superior characteristics compared to, for example, HP- $\beta$ -CD" (column 4, lines 26 to 28). In other words, this document shows that the selection of the particular cyclodextrin is important with respect to the effect of a given cyclodextrin with a given drug.

The Examiner's attention is also directed to enclosed U.S. Patent 6,713,461 ("Billotte"), which is primarily directed to solving the problem of nasal mucosal irritation associated with the intranasal administration of the active drug eletriptan hemisulphate with caffeine (see column 1, lines 26 to 31). Billotte accomplishes this using a formulation including SBE-CD. However, Billotte also illustrates the unpredictable nature of cyclodextrins. At column 1, lines 55 to 57, it is stated that SBE-CD "undesirably and unpredictably decreases the aqueous solubility of eletriptan, or a salt thereof." Despite the good intranasal toleration using SBE-CD with eletriptan, this negative teaching regarding the decrease in solubility is a clear teaching away from the present invention. One skilled in the art searching for the effects of SBE-CD on drugs would have been discouraged by Billotte even from trying to use SBE-CD to enhance the aqueous solubility of a drug. This reference demonstrates that the unpredictability of the effect of SBE-CD on a particular drug cannot be merely ignored, or even worse, such unpredictability was attempted to be refuted by the Examiner by picking and choosing only certain beneficial properties from only certain selected references were used against the present invention.

The present inventors have surprisingly found that SBE-CD is particularly suitable for enhancing the solubility of zolpidem. This was not an obvious choice, particularly given the unpredictable nature of various cyclodextrins, and especially SBE-CD. The results presented in

Table 1 at page 16 of the present application show that SBE-CD provided surprisingly better improvements in solubility than two other cyclodextrins tested, hydroxypropyl- $\beta$ -cyclodextrin and a methylated- $\beta$ -cyclodextrin.

There are also significant commercial reasons why the skilled person would not have obviously selected SBE-CD. This material is a proprietary material and is costly compared to other cyclodextrins. If Applicants had been able to achieve comparable results using another more widely available and cheaper cyclodextrin they would not have chosen SBE-CD in preference.

The inclusion of chitosan in the compositions of the invention is also vitally important, and as noted in paragraph 10 of Dr. Castile's Declaration, such inclusion further complicates the unpredictability of compositions containing cyclodextrins such as SBE-CD. The results in Table 3 at page 19 of the present application show that while SBE-CD may increase the solubility of zolpidem, it does not provide a composition with a useful drug bioavailability. The introduction of chitosan significantly enhanced the bioavailability, and the combination of chitosan with SBE-CD along with zolpidem or other intranasally-administered drug has not been disclosed previously.

It is also clear from a comparison of the information in the last paragraph at page 8 of the present application and the information at page 6, lines 7 to 10, that the inclusion of chitosan in the compositions of the invention places a restriction on the pH of the composition. In the absence of chitosan, the pH may be from 3 to 8 (see page 6, line 7). However, a narrower range of 3.5 to 6.5 is specified in claim 37 for the chitosan containing compositions of the invention.

It would not have been obvious to the skilled person in view of the cited prior art to select all of the parameters needed to provide the advantageous compositions of the presently-claimed invention.

The references cited in the Office Action will now be discussed and distinguished from the present invention.

***U.S. Patent Application Publication No. 2004/0241100 ("Kramer")***

The Examiner has used Kramer as the primary reference in two of the obviousness rejections and as a secondary reference in other obviousness rejections.

Kramer describes compositions for nasal administration which comprise zolpidem, a prodrug thereof, a pharmaceutically acceptable salt thereof, or a combination thereof and a pharmaceutically acceptable nasal liquid carrier in liquid form. There is a suggestion in paragraph [0036] of Kramer that the compositions described therein could comprise chitosan. However, there is no explicit disclosure of a composition that actually contains chitosan. The Examiner has maintained the position that the use of chitosan would have been obvious from the disclosure of Kramer. Even if one were to accept this, which Applicants do not, only for the sake of argument, there is nothing in Kramer to suggest that up to 20 mg/ml of chitosan would be a suitable amount in any solution for the intranasal delivery of zolpidem, let alone that this is the amount that should be used for a solution comprising the specific cyclodextrin, SBE-CD, as presently claimed.

Some of the assumptions that the Examiner made based on the disclosure of Kramer are incorrect. At page 5 of the Detailed Action, the Examiner suggested that Kramer discloses compositions comprising from 0.01 to 250 mg zolpidem in a carrier having a volume of from 0.02 to 4 ml and that this provides a teaching of a concentration of from 0.5 to 62.5 mg/ml. To reach this conclusion, the Examiner has combined the teaching of paragraphs [0023] to [0026] of Kramer.

In paragraph [0024], Kramer states that from about 0.01 mg to about 250 mg of active ingredient per day may be delivered as a single once-a-day dose or in doses administered two, three or four times a day.

In paragraph [0025], it is stated that the dose unit volume is preferably from 0.001 ml to 4 ml. The range of 0.5 to 62.5 mg/ml that the Examiner has quoted seems to be based on the assumption that 0.001 mg of zolpidem is contained in 0.002 ml of carrier and that 250 mg of zolpidem is contained in 4 ml of carrier. This is a gross over-simplification and a misrepresentation of what Kramer teaches.

A composition comprising 250 mg of zolpidem in 4 ml of carrier would only be required if one were to attempt to administer the maximum daily dose of zolpidem taught by Kramer as a once daily dose. There is absolutely no indication that 250 mg of zolpidem would be or could be administered in a once-a-day dose or that it would be practically possible to produce a composition comprising zolpidem in a concentration required to achieve this.

In fact, one could take the Examiner's reasoning even further to another illogical conclusion and argue that the maximum concentration disclosed in Kramer is 250 mg of zolpidem in 0.001 ml of carrier. This would result in the ridiculous figure of 250,000 mg/ml of zolpidem in a once-a day dose.

There is nothing in Kramer to suggest that the upper end of the range in paragraph [0024] is associated with the upper end of the range in paragraph [0025]. The Examiner's conclusion seems to be to be flawed by this unwarranted assumption.

In any event, in view of the information provided in paragraph [0026] of Kramer, it is not necessary to conduct the type of analysis that the Examiner must have conducted to identify the ranges specified in the Office Action. In paragraph [0026], it is stated that the preferred weight/weight loading of the active ingredient of Kramer's compositions range from 0.003 to 95% by weight, based on the total weight of the composition. Assuming a water vehicle, these would approximate to zolpidem concentrations in the range of 0.3 to 950 mg/ml.

As discussed at page 3, lines 24 to 28, of the present application, the reported saturated aqueous solubility of zolpidem tartrate is 23 mg/ml. This is the saturated solubility of the drug and only lower concentrations are practically achievable in pharmaceutical formulations. This is because a solution comprising the drug at or near the saturated concentration would be unstable. See paragraph 18 of Dr. Castile's Declaration. Changes in temperature or other storage conditions could result in precipitation of the drug. Clearly, in the absence of a solubility enhancer not disclosed or even suggested as a critical component, it would not be feasible to provide a composition having a concentration of zolpidem within the vast majority of the range suggested in Kramer.

There is no indication in Kramer as to how one might increase zolpidem solubility to produce practically useful nasal formulations, which have a suitable concentration of zolpidem

and remain stable with no drug precipitation on storage. It is also noted that the range provided in paragraph [0026] of Kramer is very broad. There is no information in Kramer that would have suggested to the skilled person that the optimum zolpidem concentration for a nasal composition would be within the concentration range specified in claim 37 of the present application. Merely indicating that Applicants' claimed range might be encompassed within a very considerably larger range denigrates the careful selection aspect of this range as part of the present invention.

Likewise, the pH range given in paragraph [0038] of Kramer of from about 3 to about 10 is much broader than the range recited in claim 37. There is no information in Kramer to suggest that a pH range of from 3.5 to 5.6 would be most appropriate for any composition, let alone a composition comprising 1 to 20 mg/ml of the chitosan and 50 to 400 mg/ml of SBE-CD, and again ignores the important selection aspect of the pH range of claim 37.

It is also clear from claim 13 of Kramer that Kramer is not concerned exclusively with producing sprayable compositions. Thus, there is nothing in Kramer to encourage the skilled person to produce a composition having a viscosity less than 150 cp rather than, for example, a very considerably higher viscosity as would be used in a syrup, gel or ointment containing zolpidem within the scope of Kramer's disclosure.

It is clear from the above discussion that the teaching of Kramer falls a long way short of the teaching of the present invention. It is not simply a case of adding a cyclodextrin to the compositions of Kramer to arrive at the present invention.

As will be explained below, none of the other cited documents provide all of the information that the skilled person would have needed in order to arrive at the present invention.

***European Published Application Publication No. EP 1250925 A2 ("Auh")***

In both of the obviousness rejections in which the Examiner has used Kramer as the primary reference, Auh was cited and applied as a secondary reference.

Auh describes an antiemetic nasal spray composition comprising ondansetron hydrochloride and a base material consisting of (i) 70 to 80% by weight of water, (ii) 5 to 15% by weight of polyethylene glycol, (iii) 0.005 to 0.02% by weight of benzalkonium chloride and



(iv) 7 to 20% by weight of one stabilizer selected from sulfobutyl ether  $\beta$ -cyclodextrin sodium salt, dimethyl- $\beta$ -cyclodextrin and 2-hydroxypropyl- $\beta$ -cyclodextrin.

The Examiner's reliance on Auh seems to be based on an assumption that all cyclodextrins can be treated equally as solubility enhancers. This is simply not the case, as noted above and in Dr. Castile's Declaration. As discussed above, the properties of cyclodextrins are not predictable. Not all cyclodextrins will improve the solubility of all drugs. While all three cyclodextrins listed in Auh may, at least to some degree, enhance the solubility of ondansetron when used in combination with other essential ingredients of Auh's base, this does not mean that all these cyclodextrins will give the required enhancement of solubility for zolpidem. In fact, as discussed above and as shown in Table 1 at page 16 of the present application, hydroxypropyl- $\beta$ -cyclodextrins and methylated cyclodextrins do not give the required enhancement of solubility. The drug and the cyclodextrin have to be carefully matched and it is not predictable which cyclodextrins will be effective to enhance the solubility of which drugs. Auh does not teach the skilled person how to match zolpidem to a suitable cyclodextrin. Still less does it teach how to optimize the other parameters specified to claim 1 of the present application in order to produce a composition particularly suitable for the intranasal delivery of zolpidem.

***U.S. Patent 6,699,849 ("Lofsson") and Nasal Drug Delivery: New Methods and Strategies, Drug Discovery Today, Vol. 7, No. 23, December 2002 ("Illum 2002")***

Lofsson describes cyclodextrin complexes of benzodiazepines and methods for enhancing a complexation efficiency of a drug with cyclodextrin and for enhancing the availability of a drug following administration of a cyclodextrin-drug complex.

The Examiner referred to column 4, lines 6 to 8, and stated that Lofsson teaches that cyclodextrins can act as penetration enhancers by increasing drug bioavailability at the surface of the biological barrier. This may be true in some circumstances but it is not a universally correct statement. There is a document currently of record and cited by the Examiner, namely Illum 2002, that clearly teaches that cyclodextrins are not reliable penetration enhancers in compositions for human use. The Examiner seems to have overlooked or ignored the teaching of

Illum 2002, which clearly teaches away from the use of cyclodextrins as absorption enhancers in compositions for human use.

Illum 2002 makes it clear that cyclodextrins are not necessarily penetration enhancers. The Examiner has indicated that Illum teaches that cyclodextrins are effective absorption enhancers. To come to this conclusion, the Examiner's reading of Illum 2002 must have been very selective. The Examiner referred to the second column at page 1186 of Illum 2002 as disclosing the absorption enhancing abilities of dimethyl- $\beta$ -cyclodextrin. However, what Illum 2002 actually discloses in this paragraph is that dimethyl- $\beta$ -cyclodextrin acts as an absorption enhancer when it is used in a rat model but almost zero bioavailability was achieved when the same formulation was tested in rabbits and in man. This conclusion is also summarized in the first column at page 1188 under the heading cyclodextrins where it is stated "cyclodextrin derivatives for nasal absorption enhancement have shown early promise in animal models, but, unfortunately, this has not been confirmed in humans. These cyclodextrins systems, are, however, still used in nasal formulations but mainly as a means of providing drug solubilisation".

This teaching away from the use of dimethyl- $\beta$ -cyclodextrin for use in a composition for humans in Illum 2002 would have actively discouraged the skilled person from considering using this or other cyclodextrins as absorption enhancers for compositions for human administration of drugs.

Also enclosed is a further document that highlights the inconsistent and unpredictable properties of cyclodextrins: Merkus *et al*, "Cyclodextrins in Nasal Drug Delivery", *Advanced Drug Delivery Reviews*, 36, 1999, pp. 41-57) ("Merkus"). The information in Table 1 of Merkus shows that the effect that cyclodextrins have on bioavailability is far from predictable. The effects seen can depend on the nature of the drug, the nature of cyclodextrin, the concentration of the cyclodextrin and the species to which the drug is administered. For example, in the case of the drug buserelin, in rats some cyclodextrins increased bioavailability significantly, some increased bioavailability a little and others decreased bioavailability. In the case of ACTH (4-9) analogue (Org2766) the cyclodextrins tested increased the drug bioavailability to varying extents in rats and to only to a small extent in rabbits. In the case of leuprolide the effect seen in rats was not consistent and there was a significant reduction in bioavailability in humans.

The conclusions of Merkus are clear. In some cases, methylated  $\beta$ -cyclodextrins can be useful excipients in nasal drug delivery, but care has to be taken due to interspecies variations. It most certainly cannot be concluded that the skilled person would use a given cyclodextrin, such as SBE-CD, in the expectation that it would enhance bioavailability of all drugs in humans.

The Examiner's conclusion based on the teaching of Loftsson (and separately based on the teaching of Illum 2002) that cyclodextrins are an obvious choice as penetration enhancers is contrary to the teaching in the art at the priority date, including the teaching of record.

The fact that cyclodextrins are not effective penetration enhancers is confirmed by experiments conducted by the Applicants and included in the present application as filed. Table 3 at page 19 of the present application reports the results of a study of the pharmacokinetic parameters obtained following intranasal administration of a zolpidem solution comprising SBE-CD both in the absence and presence of chitosan. It can be seen that when the composition of Example 3, which did not comprise chitosan, was used, the bioavailability and the  $C_{max}$  were both low. These values indicate that SBE-CD alone does not enhance the absorption of zolpidem and does not provide a practical composition for the intranasal delivery of zolpidem. The results of this study are consistent with the information provided in Illum 2002 and Merkus and are contrary to the Examiner's assertion that cyclodextrins are necessarily penetration enhancers.

The study whose results are reported in Table 3 of the present application was conducted on sheep. Sheep provide a good model for intranasal delivery in humans. Sheep are a significantly better model for humans than rats. The suitability of sheep as a model for nasal delivery in humans (and the unsuitability of rats) is discussed in the enclosed copy of Illum, "Nasal Delivery, The Use of Animal Models to Predict Performance in Man", *Journal of Drug Targeting*, Vol. 3, 1996, pp 427 - 442 ("Illum 1996"). See particularly, the last sentence in the section on sheep at the top of page 436 and the conclusion in Illum 1996.

***PCT Publication WO 03/095496 (in Japanese) and US Patent Application Publication No. 2005/0215520 ("Liu")***

The Examiner referred to Liu as the primary reference in the obviousness rejection that starts at the bottom of page 8 of the Detailed Action.

Liu describes a process for preparing a water-soluble complex of water-insoluble or sparingly-soluble organic medicines and  $\beta$ -cyclodextrin derivatives. There is no disclosure or suggestion of the use of SBE-CD. As discussed above, the properties of cyclodextrins vary and the information provided in Liu cannot be considered to provide any teaching relevant to SBE-CD.

The Examiner referred to Example 2 of Liu as disclosing a formulation comprising zolpidem and a cyclodextrin derivative. However, it appears that the reference to Example 2 (disclosing a formulation using artesunate as the drug) was a mistake and that the Examiner intended to refer to Example 12, which describes a process for preparing a complex of zolpidem-hydroxide propyl- $\beta$ -cyclodextrin (HP- $\beta$ -CD) in ethanol followed by recovery as a solid material. This example is a simple synthesis example that teaches how to prepare a complex of zolpidem-HP- $\beta$ -CD, but it does no more than this. It does not teach or suggest how to prepare a composition for intranasal delivery. Except for the use of zolpidem, Liu's Example 12 (and the rest of Liu) most certainly does not disclose or suggest any of the other essential ingredients or concentrations, pH and viscosity recited in claim 37 of the present application.

It must further be noted that the cyclodextrin used in Example 12 of Liu is not suitable for use in the present invention. It is essential that SBE-CD is used in the present invention and the inventors have performed experiments that show that the cyclodextrin used in Example 12 of Liu is not suitable for use in the present invention. The data in Table 1 of the present application show that HP- $\beta$ -CD was unable to enhance the solubility of zolpidem tartrate to the degree required by the present invention. Thus, all that Example 12 of Liu does is tell the skilled person how to make a complex that is not suitable for use in the present invention. No information about the properties of SBE-CD is given. There is therefore nothing in Liu that would have motivated the skilled person to use SBE-CD.

There is also nothing in Liu to suggest that chitosan could be or should be used in compositions for the intranasal delivery of zolpidem.

In summary, Liu does not contain any information that is relevant to the present invention and most certainly does not provide any information that would have motivated or enabled the skilled person to prepare a composition as now claimed. Liu is therefore not a suitable document

for use as a primary reference, or even a secondary reference as a basis for any obviousness rejection of the claimed subject matter.

***PCT Publication WO 03/080021 ("Birch")***

The Examiner has combined the teaching of Birch with the combination of Kramer and Auh or the combination of Liu and Illum. Birch does not provide the information that is missing from either of these combinations, even assuming, without agreement, only for the sake of argument that the combinations with or without Birch are appropriate to even make.

Birch describes compositions for the intranasal administration of the analgesic drug buprenorphine. This drug is completely different compared to zolpidem, as shown in Exhibit D to Dr. Castile's Declaration. This is important, as noted above and as set forth in paragraph 21 of Dr. Castile's Declaration, evidencing the unpredictability of the effect of cyclodextrins, including SBE-CD, and chitosans on zolpidem in view of the differences between zolpidem and buprenorphine.

The Examiner seems to have relied on Birch solely as teaching that chitosan can be used in compositions for intranasal drug delivery and that the chitosan may be in the form of chitosan glutamate and used in an amount within the range specified in claim 16. This is taking the information of Birch completely out of context. Just because that amount of chitosan glutamate is suitable for use in a composition comprising the unrelated drug buprenorphine and comprising other ingredients that do not consist essentially of the components, with the claimed concentration, pH and viscosity of the composition of the present invention, it cannot be assumed that this amount of chitosan is suitable for use with zolpidem, let alone a zolpidem composition comprising 50-400 mg/ml of SBE-CD.

As is clear from the comments above, the combinations of Kramer and Auh, as well as Liu and Illum 2002 fall very short of providing the information and motivation that the skilled person would have needed to arrive at the present invention. The information missing from these combinations does not solely relate to the inclusion of chitosan in the compositions. Thus, Birch cannot provide all of the missing information.

**Comments Concerning Dr. Castile's Declaration**

At pages 14-15 of the Detailed Action, the Examiner discounted Dr. Castile's Declaration and its evidence of unexpected and unpredictable results of the present invention, apparently because it did not assertedly contain a side-to-side comparison between the closest prior art and the present invention. In the discussion regarding Dr. Castile's Declaration, the Examiner pointed out the various elements selectively picked and chosen from the various references and artificially combined to formulate the obviousness rejections.

Applicants' respectfully, but strenuously, submit that the Examiner overlooked the main points of Dr. Castile's Declaration and its exhibits. The Examiner, both before and after Dr. Castile's Declaration, has taken the position that various components can be selected from the references and combined, apparently simply because the components existed before the present invention, and that it would have been obvious at the time of the present invention to combine them, resulting in Applicants' invention. Dr. Castile's Declaration refutes any asserted reasonableness of doing so, and points out the unpredictability of the effect of the use of various cyclodextrins and various chitosans with various drugs. As noted generally in paragraphs 8-10, 15-19 and 21, bolstered by the specific comparison of the effects on ondansetron (Auh's drug) of cyclodextrins and chitosan in paragraphs 11-14, Dr. Castile's Declaration clearly explained why it is important to know the interaction of different drugs with different cyclodextrins and different chitosans, and what may appear to be efficacious combinations of ingredients with one drug often are not efficacious with another drug, and with different types of cyclodextrins and the presence or absence of chitosan. More specifically, Dr. Castile's Declaration established that there is no disclosure in the prior art of anyone previously using or suggesting the use of SBE-CD and chitosan together with zolpidem, or what the likely effect of doing so would be.

In essence, Dr. Castile's Declaration clearly evidenced the unpredictability of making the combination that the Examiner did. The Examiner's assertions of predictability have been effectively rebutted by the evidence presented in Dr. Castile's Declaration, which cannot be ignored. Moreover, the evidence of unpredictability of the use and effect of SBE-CD and chitosan on zolpidem as explained above with respect to the additional references submitted with this Amendment further buttresses the actual unpredictability and non-obviousness of the present

invention compared to the prior art, even assuming only for the sake of argument without agreement, that one skilled in the art would have located and combined the references as the Examiner has done. Such selection and combination, and the selection from among the references of isolated asserted teachings is just the type of hindsight based only on the present application that the evidence presented herein and in Dr. Castile's Declaration overcomes.

Reconsideration and withdrawal of all of the rejections, a rejoinder of the non-provisionally elected claims, and an early Notice of Allowance are respectfully requested.

Respectfully submitted,

**Jonathan David CASTILE, et al.**

April 15, 2011  
(Date)

By: \_\_\_\_\_



**ALAN S. NADEL**

Registration No. 27,363

**PANITCH SCHWARZE BELISARIO & NADEL LLP**

One Commerce Square

2005 Market Street, Suite 2200

Philadelphia, PA 19103-7013

Telephone: 215-965-1330

**Direct Dial: 215-965-1280**

Facsimile: 215-965-1331

E-Mail: [anadel@panitchlaw.com](mailto:anadel@panitchlaw.com)

Enclosures